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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,870	11/16/2005	Benny Bang-Andersen	435-US-PCT	2040
45821	7590	11/21/2007	EXAMINER	
LUNDBECK RESEARCH USA, INC.			O DELL, DAVID K	
ATTENTION: STEPHEN G. KALINCHAK, LEGAL			ART UNIT	PAPER NUMBER
215 COLLEGE ROAD			1625	
PARAMUS, NJ 07652			MAIL DATE	
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			PAPER	

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	10/551,870	BANG-ANDERSEN ET AL.
Examiner	Art Unit	
David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 05 September 2007.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-16, 18, 20, 22, 24 and 26-34 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1-16, 18, 20, 22, 24 and 26-34 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner. Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a). Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some \* c) None of:
  1. Certified copies of the priority documents have been received.
  2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 5 March 2007.
- 4) Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) Notice of Informal Patent Application
- 6) Other: \_\_\_\_\_.

**DETAILED ACTION**

1. Claims 1-16, 18, 20, 22, 24, 26-34 are pending in the current application.
2. This application is a national stage of PCT No. PCT/DK04/00241, filed April 2, 2004 which claims the benefit of U.S. Provisional Application No. 60/460,265, filed April 4, 2003 which claims the benefit of foreign priority under 35 U.S.C. §119(a)-(d) of Danish Application No. PA 2003 00519, filed April 4, 2003.

**Response to Arguments**

3. Applicant's arguments filed on September 5, 2007, have been fully considered and are persuasive in part and non-persuasive in part. Each response to each rejection will be discussed in turn. The objection to the specification is withdrawn in light of the amendments. The double patenting rejection over U.S. 7,144,884 is maintained for the reasons of record, since applicant's arguments that the '884 application is not prior art are spurious. The date of the patent/application is immaterial to a double patenting rejection, as only one patent may be obtained for one invention regardless. Moreover the argument that the '884 patent does not define Y in the claims and the examiner improperly imported the definition from the spec into the claims, is spurious since the definition of Y is not delineated in the claims, and applicant's use terms idiosyncratically, the examiner must look to the specification for the meaning of the term. The only other interpretation of the term Y is that for the element Yttrium, however this is a chemical impossibility and clearly not what was meant by the claims. Based on the applicant's amendments the statutory double patenting rejection over the '188 application, is now an obviousness type double patenting rejection. The rejection of claims 1-13, 15, 20, 22, 24, 26-31 under 112 1<sup>st</sup> paragraph for scope of enablement is withdrawn based on applicant's

amendments. The rejection of claims 18, 32-34 for lack of enablement is maintained for the reasons of record. The examiner clearly showed that no clear nexus exists between the assays of the specification and the treatment claims of the instant case, by referring the applicant to the appropriate literature.

With respect to the rejection under 35 U.S.C. 103 (a) for obviousness, the rejection of the remaining claims is maintained for the reasons of record. The applicant has argued that there is no suggestion to combine the references, and the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Elliot clearly teaches a positions isomer, moreover Wang and others teach that the 4-postion isomers are well-known in this very narrow art to have the desired activity. One of ordinary skill is also one of "ordinary creativity, not an automaton". See *Leapfrog Enterprises Inc. v. Fisher-Price. and Mattel Inc.* UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT "An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at 12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

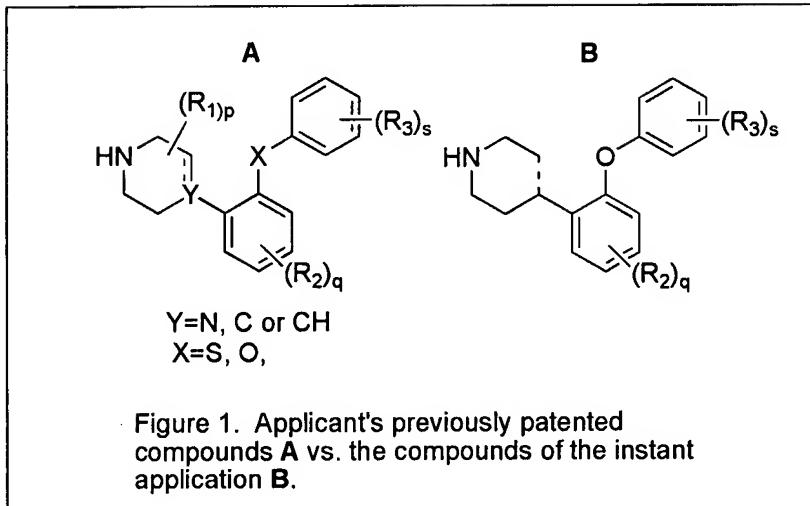
### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-16, 18, 20, 22, 24, 26-34 are rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6-11 of U.S. Patent No. 7,144,884 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '834 patent clearly claims the Markush of the instant case as well methods of using the compounds in the treatment of depression and various disorders.



The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness are summarized as follows:

- A) Determining the scope and contents of the prior art.
- B) Ascertaining the differences between the prior art and the claims at issue.
- C) Resolving the level of ordinary skill in the pertinent art.
- D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

A) The prior art (the '884 patent) discloses the compounds of the instant case by its Markush claims 1 and 7. In this case structure **A** of Figure 1 applicant has not defined Y or X in claim 1 and thus we must see these as being the definitions of the specification as delineated in Figure 1 ( $Y=N, C \text{ or } CH$ ;  $X=S \text{ or } O$ ). Claim 7 still fails to define Y, but lets us know that  $X=O$  or  $S$ .

B) The generic structure of the '884 patent **A** and the generic structure of the instant case **B** clearly overlap, see Figure 1. The prior disclosed invention encompasses the instant claims at hand.

C) The level of ordinary skill is of little consequence. A person who has taken an introductory organic chemistry would recognize that the Markush structure of the instant case are contained by the Markush structure of the '884 patent.

D) Considering the evidence at hand here the overlapping structure of the '884 patent and the instant case, an obviousness type double patenting rejection is appropriate.

As was stated in *Ex parte WESTFAHL* 136 USPQ 265 1962, "If only one inventive concept is present, two patents cannot properly be granted, regardless of the scope or relationship of the claims, or of the order in which the applications were filed or the claims presented..... Even though an application is filed on a different species from the species already patented, a second patent may not properly be granted unless the second species is patentable over the first species.

See *In re Borcherdt et al.*, 39 CCPA 1045, 1952 C.D. 361, 665 O.G. 991, 197 F.2d 550, 94 USPQ 175 , and the cases collected in *Ex parte Robinson*, 121 USPQ 613....a generic invention could spawn a plethora of species patents....", which goes on to describe the absurdity of obtaining separate patents for chemical processes drawn toward using various isomers of xylene as solvents. Please note that the individual compounds of the invention are not being rejected here, it is only the Markush claim and all dependent claims that are at issue here.

5. Claims 1-16, 18, 20, 22, 24, 26-34 are rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 8-17 of U.S. Patent No. 7,138,407 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '407 patent clearly claims the same Markush of the instant case as well methods of using the Markush compounds in the treatment of depression and various disorders. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148

USPQ 459 (1966), that are applied for establishing a background for determining obviousness are summarized as follows:

- A) Determining the scope and contents of the prior art.
- B) Ascertaining the differences between the prior art and the claims at issue.
- C) Resolving the level of ordinary skill in the pertinent art.
- D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

- A) The claims of the '407 patent discloses the generic structure via Markush structure A (Figure1). In this case Y= C, X may be O or S.
- B) There is little difference between the generic structure of the '407 patent and the generic structure of the instant case, see Figure 1. In the '407 patent the Y group is C and the unspecified bond is a double bond, this is just the same as the instant case where a double bond is in the piperidine ring, X may be O or S (structure A Figure 1). In the instant case applicant has claimed both the single and double bond and of course X=O S (structure B Figure 1). Thus the Markush of the instant case are clearly contained in the prior filed applications Markush.
- C) The level of ordinary skill is of little consequence. A person who has taken an introductory organic chemistry would recognize that the Markush structure of the instant case are contained by the Markush structure of the '884 patent.
- D) Considering the evidence at hand here an obviousness type double patenting rejection is appropriate. Considering the evidence at hand here the overlapping structure of the '884 patent and the instant case, an obviousness type double patenting rejection is appropriate. As was stated in *Ex parte WESTFAHL* 136 USPQ 265 1962, "If only one inventive concept is present, two patents cannot properly be granted, regardless of the scope or relationship of the claims, or of the order in which the applications were filed or the claims presented..... .Even though an

application is filed on a different species from the species already patented, a second patent may not properly be granted unless the second species is patentable over the first species. See *In re Borcherdt et al.*, 39 CCPA 1045, 1952 C.D. 361, 665 O.G. 991, 197 F.2d 550, 94 USPQ 175 , and the cases collected in *Ex parte Robinson*, 121 USPQ 613....a generic invention could spawn a plethora of species patents....”, which goes on to describe the absurdity of obtaining separate patents for chemical processes drawn toward using various isomers of xylene as solvents in what would be identical processes. Please note that the individual compounds of the invention are not being rejected **here**, it is only the Markush claim and all dependent claims that are at issue here.

6. Claim 1-16, 18, 20, 22, 24, 26-34 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-10, 12-14, 17, 19, 21, 23, 25, 27, 29, 31-34 of copending Application No. 11/551,188. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. The claims are coextensive in scope for reasons outlined above.

7. Claims 1-16, 18, 20, 22, 24, 26-34 are rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims of U.S. patent 7,138,238 (previously cited as the ‘238 patent). Although the conflicting claims are not identical, they are not patentably distinct from each other because the ‘238 patent clearly claims the Markush of the instant case as well methods of using the compounds in the treatment of depression and various disorders. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness are summarized as follows:

- A) Determining the scope and contents of the prior art.
- B) Ascertaining the differences between the prior art and the claims at issue.

Art Unit: 1625

- C) Resolving the level of ordinary skill in the pertinent art.
- D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

A) The prior art (the '238 patent) discloses the Markush structure **A** Figure 1, Y=CH, and X=S or O.

B) There is little difference between the Markush claims of the '238 patent and the instant case, see Figure 1. In the '238 patent the Y group is CH and the unspecified bond is single, this is just the same as the instant case where a single bond is in the piperidine ring (structure **B** Figure 1). The instant claim encompasses the prior filed application in part and vice versa.

C) The level of ordinary skill is of little consequence. A person who has taken an introductory organic chemistry would recognize that the Markush structure of the instant case are contained by the Markush structure of the '238 patent.

D) Considering the evidence at hand here the overlapping structure of the '884 patent and the instant case, an obviousness type double patenting rejection is appropriate. As was stated in *Ex parte WESTFAHL* 136 USPQ 265 1962, "If only one inventive concept is present, two patents cannot properly be granted, regardless of the scope or relationship of the claims, or of the order in which the applications were filed or the claims presented..... Even though an application is filed on a different species from the species already patented, a second patent may not properly be granted unless the second species is patentable over the first species. See *In re Borcherdt et al.*, 39 CCPA 1045, 1952 C.D. 361, 665 O.G. 991, 197 F.2d 550, 94 USPQ 175 , and the cases collected in *Ex parte Robinson*, 121 USPQ 613....a generic invention could spawn a plethora of species patents....", which goes on to describe the absurdity of obtaining separate patents for chemical processes drawn toward using various isomers of xylene as solvents in what would be

identical processes. Please note that the individual compounds of the invention are not being rejected **here**, it is only the Markush claim and all dependent claims that are at issue here.

Considering the evidence at hand here an obviousness type double patenting rejection is appropriate. Considering the evidence at hand here the overlapping structure of the '884 patent and the instant case, an obviousness type double patenting rejection is appropriate. As was stated in *Ex parte WESTFAHL* 136 USPQ 265 1962, "If only one inventive concept is present, two patents cannot properly be granted, regardless of the scope or relationship of the claims, or of the order in which the applications were filed or the claims presented..... Even though an application is filed on a different species from the species already patented, a second patent may not properly be granted unless the second species is patentable over the first species. See *In re Borcherdt et al.*, 39 CCPA 1045, 1952 C.D. 361, 665 O.G. 991, 197 F.2d 550, 94 USPQ 175 , and the cases collected in *Ex parte Robinson*, 121 USPQ 613....a generic invention could spawn a plethora of species patents....", which goes on to describe the absurdity of obtaining separate patents for chemical processes drawn toward using various isomers of xylene as solvents in what would be identical processes. Please note that the individual compounds of the invention are not being rejected **here**, it is only the Markush claim and all dependent claims that are at issue here.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 18, 32-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The only information given as to what these compounds may do, at least in the pharmacological sense, is on pg. 33 of the disclosure "Results of the experiments showed that the tested compounds of the invention inhibit the norepinephrine and serotonin [sic] reuptake with  $IC_{50}$  below 200nM". Is this for both assays for all compounds? Applicant seems to believe that these compounds are useful for "treating affective disorders". One "affective disorder" that applicant has claimed is depression. In a recent review on the subject of monoamine reuptake inhibitors (Thorsten et. al. *Drug Discovery Today* 2004, 1(1) 111-116, pg. 138) states:

" Whether novel monoamine reuptake inhibitors with different monoamine ratios would give a better efficacy is still not known. Hitherto, the least evaluated option is a combination of 5-HT, NA, DA and monoamine reuptake inhibition. This combination could give an accelerating treatment response or increased efficacy in otherwise treatment-resistant depressed patients. An elimination of SSRI-like side effects might be possible, although the risk for DA related side effects should be considered. Large conclusive clinical trials will be the only option to guide further drug discovery of monoamine transporters."

The examiner wonders what the effects on dopamine transport are, as this could play a major role in the clinical application. The similarity of these compounds to cocaine, make these compounds liable for abuse, and few physicians would argue that cocaine, while elevating mood, is a good treatment for depression or affective disorders. In addition, procaine, a local anesthetic, is known to inhibit monoamine uptake using assays similar to the ones described (Sato, et. al. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 2000, 361, 214-220, entire document), yet it has not been shown to be efficacious for the treatment of depression or anxiety disorders, and one would have serious doubts that a medical doctor would use procaine in such a manner.

Disclosure of the activity of the compounds and dosages that are critical or essential to the practice of the invention, but not included in the claims is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). Applicant claims that these compounds are useful for “anxiety disorders”. However a recent review (Milan, M. J. *Progress in Neurobiology* 2003, 70, 83-244 pg. 13) states:

“With one exception in mice (Hascoët et al., 2000), acute administration of SSRIs or 5-HT/NA reuptake inhibitors **has proven to be ineffective or to increase anxiety** in the VCT and other conflict procedures, mirroring above-mentioned clinical and experimental observations (Table 16 and Fig. 7) (Mason et al., 1987; Fontana and Commissaris, 1988; Fontana et al., 1989a; Kostowski et al., 1994; Beaufour et al., 1999; Borsini et al., 2002). In certain conflict paradigms, it has been shown that chronic treatment is accompanied by the progressive induction of anxiolytic effects (Fontana and Commissaris, 1988; Fontana et al., 1989a; Beaufour et al., 1999; Borsini et al., 2002) and, assuming its appropriate manipulation to detect acute anxiogenic actions of SSRIs and 5-HT/NA reuptake inhibitors, such studies would be of interest to undertake with the VCT.”

Thus this seems to say that at least in animal models compounds with the same purported mechanism cause anxiety. Furthermore it is not clear, what these compounds will do in such complex disease states, and one cannot predict *a priori* what the outcome of such complex pharmacological behavior would be in the complex diseases of claims 18, 32-34. The “how to use” requirement of 35 U.S.C. 112 are not met by disclosing a pharmacological activity of the claimed compounds if one skilled in the art would not be able to use the compounds effectively without undue experimentation (In re Diedrich (CCPA 1963) 318 F2d 946, 138 USPQ 128; In re Gardner et. al. (CCPA 1970) 427 F2d 786, 166 USPQ 138). One cannot believe that these compounds will behave as therapeutics in those suffering from depression/anxiety disorders. It

seems very unlikely that a medical doctor would know what to do with these compounds. Given the mechanism that applicant alleges and the current knowledge in the art no method of use is enabled. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a):

“A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the “...”claimed invention without undue experimentation. *In re Wright* 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” It is very clear that one could not make/use this invention that has no working examples in this unpredictable art without undue experimentation.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

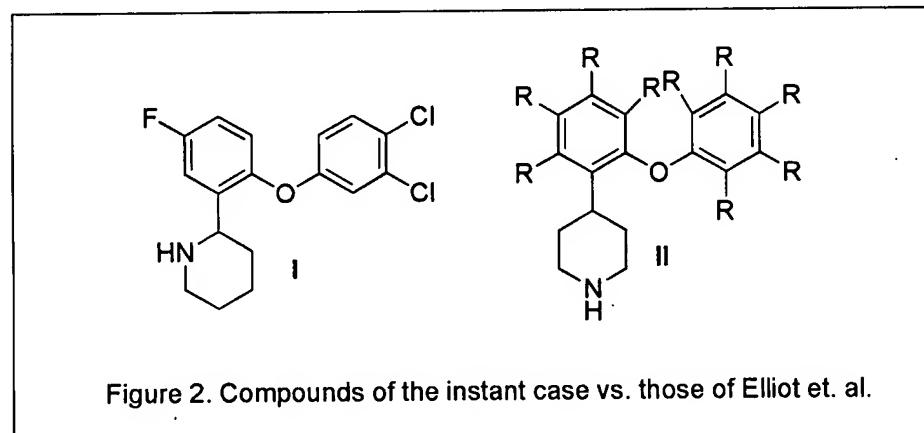
9. Claims 1-13, 15, 20, 22, 24, 26-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elliot et. al. PCT/IB00/00108 in view of Wang S., et. al. *J. Med. Chem.* 2000, 43, 351–360 or Tamiz A.P, et. al. *J. Med. Chem.* 2000, 43, 1215–1222 or Sakamuri S, et. al. *Bioorg. Med. Chem. Lett.* 2001, 11, 495–500.. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

A) Determining the scope and contents of the prior art.

Art Unit: 1625

- B) Ascertaining the differences between the prior art and the claims at issue.
- C) Resolving the level of ordinary skill in the pertinent art.
- D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

Elliot et. al. disclose 2-[2-(3,4-dichlorophenoxy)-5-fluorophenyl]-piperidine I on pg. 9 line 13, which has the same utility of the instant case (inhibition of monoamine reuptake); shown side-by-side with applicant's structure II in Figure 2.



These are clearly position isomers. The compounds of Elliot et. al. PCT/IB00/00108 are 2-aryloxy-piperidines and those of the instant case are 4-aryloxy-piperidines. The only difference here is the position of the biaryl ether on the piperidine ring (2 in the '108 application and 4 in the instant case). One of ordinary skill in the art is one with experience in medicinal chemistry and pharmacology and knows the basics of drug design. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these position isomers based on the expectation that such close analogues would have similar properties and upon the routine nature of such position isomer experimentation in the art of medicinal chemistry. It would be routine for the chemist to vary the point of attachment in order to increase potency. The applicant would have been motivated to make the change based on the fact that 4-aryl-piperidines were well known in the art to have the desired monoamine

reuptake activity as evidenced by numerous publications: (Wang S., et. al. *J. Med. Chem.* **2000**, *43*, 351–360. Tamiz A.P, et. al. *J. Med. Chem.* **2000**, *43*, 1215–1222. Sakamuri S, et. al. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 495–500.). The opinion set forth in 16 USPQ2d 1897 *In re Dillon U.S. Court of Appeals Federal Circuit No. 88-1245 Decided November 9, 1990 919 F2d 688*: “When chemical compounds have ‘very close’ structural similarities and similar utilities, without more a *prima facie* case may be made.” In the instant case the structure is very similar and the utility is the same, thus the claims at hand of the instant case (1-15, 18, 20-34) are obvious over the prior art. Positional isomers, having the same radical on different positions of the molecule, are *prima facie* obvious, and require no secondary teaching. *In re JONES* 74 USPQ 152 (4-methyl naphthyl-1-acetic acid and 2-methyl naphthyl-1-acetic acid obvious over a reference teaching 1-methyl naphthyl-2-acetic acid), quoted with approval by *Ex parte MOWRY AND SEYMOUR* 91 USPQ 219, *Ex parte Ulliyot* 103 USPQ 185 (4-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline obvious over a reference teaching 4-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline), “[p]osition isomers are recognized by chemists as similar materials”, *Ex parte BIEL* 124 USPQ 109 (N-ethyl-3-piperidyl diphenylacetate obvious over a reference teaching N-alkyl-4-piperidyl diphenylacetate), “[appellant's arguments] do not, in any way, obviate the plain fact that appellant's DACTIL is an isomer of McElvain et al.'s compound. This close relationship places a burden on appellant to show some unobvious or unexpected beneficial properties in his compound in order to establish patentability”, *Ex parte Henkel* 130 USPQ 474, (1-phenyl-3-methyl-4-hydroxypyrazole obvious over reference teaching 3-phenyl-5-methyl-4-hydroxypyrazole), “appellants have made no comparative showing here establishing the distinguishing characteristics they allege which we might consider as evidence that the claimed

compounds are unobvious. It is clear from *In re Henze*, *supra*, and the authorities it cites, that at least this much is necessary to establish patentability in adjacent homologs and **position isomers** (emphasis added)".

*In re Surrey* 138 USPQ 67, (2,6-dimethylphenyl-N-(3-dimethylaminopropyl) carbamate obvious over a reference teaching 2,4-dimethylphenyl N-(3-dimethylaminopropyl) carbamate), *In re MEHTA* 146 USPQ 284, (2-(1-methyl)-pyrrolidylmethyl benzilate obvious over a reference teaching 3-(1-methyl)-pyrrolidylmethyl benzilate), "[t]he fact that a **position isomer** (emphasis added) of a compound is known is some evidence of the obviousness of that compound. **Position isomerism** (emphasis added) is a fact of close *structural* (emphasis in original) similarity ...".

*Deutsche Gold-Und Silber-Scheideanstalt Vormals Roessler v. Commissioner of Patents*, 148 USPQ 412, (1-azaphenothiazines obvious over references teaching 2-azaphenothiazines, 3-azaphenothiazines, and 4-azaphenothiazines), *In re Crounse*, 150 USPQ 554 (dye with *para* (CONH<sub>2</sub>) and *ortho* (OCH<sub>3</sub>) obvious over a dye with the same nucleus and *meta* (CONH<sub>2</sub>) and *para* (OCH<sub>3</sub>) group), *Ex parte Allais*, 152 USPQ 66, (3-aminopropyl-6-methoxyindole obvious over a reference teaching 3-aminopropyl-5-methoxyindole), *In re Wiechert* 152 USPQ 247, (1-methyl dihydrotestosterones obvious over a reference teaching 2-methyl dihydrotestosterones), *Monsanto Company v. Rohm and Haas Company*, 164 USPQ 556, at 559, (3',4'-dichloropropionanilide obvious over references teaching 2',4'-dichloropropionanilide and 2',5'-dichloropropionanilide), *Ex parte Naito and Nakagawa*, 168 USPQ 437, (3-phenyl-5-alkyl-isothiazole-4-carboxylic acid obvious over a reference teaching 5-phenyl-3-alkyl-isothiazole-4-carboxylic acid), "[t]his merely involves **position isomers** (emphasis added) and under the

decisions cited, the examiner's holding of *prima facie* obviousness is warranted." *In re Fouche*, 169 USPQ 429, (10-aliphatic substituted derivatives of dibenzo[a,d]cycloheptadiene obvious over reference teaching 5-aliphatic substituted derivatives of dibenzo[a,d]cycloheptadiene).

*Ex parte Engelhardt*, 208 USPQ 343 at 349, "[i]f functional groups capable of withdrawing or repelling electrons are located in the chain or **ring** (emphasis added) of a biologically active compound, transfer of such groups to other positions in which their electronic effects are lessened or enhanced may alter the biological activity of the modified compound. Hence, **position isomerism** (emphasis added) has been used as a tool to obtain new and useful drugs", *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its analogs or isomers, either geometric isomers (*cis* v. *trans*) or **position isomers** (emphasis added) (e.g. *ortho* v. *para*)".

10. Claims 1-13, 15, 20, 22, 24, 26-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martin et. al. *J. Med. Chem.* 1979, 22, 1347-1354 in view of Silverman, R.B. *The Organic Chemistry of Drug Design and Drug Action* 1992, Academic: New York, pg 19 in further view of Elliot et. al. *ibid.* The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

- A) Determining the scope and contents of the prior art.
- B) Ascertaining the differences between the prior art and the claims at issue.
- C) Resolving the level of ordinary skill in the pertinent art.
- D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

Art Unit: 1625

A) Martin et. al teach 2'-benzyl-4-phenyl-piperidines bearing a variety of *p*-substituents in the benzyl moiety (F, OMe, OH, H) and a 2'-benzyl-4-phenyl-tetrahydropyridine that are active antidepressants Martin et. al. *J. Med. Chem.* **1979**, 22, 1347-1354. The piperidines are labeled **9a, 9d-9f** and are shown in Table I pg. 1349. The 2'-benzyl-4-phenyl-tetrahydropyridine prepared is listed as compound **6h** Table III, pg 1350. In this case the assay was an animal behavior model of depression where tetrabenazine mediated effects were alleviated with the test compounds. While antagonism of the effects of tetrabenazine may proceed through a mechanism other than monoamine reuptake, the authors were careful to evaluate these compounds in a rat brain synaptosome norepinephrine reuptake inhibition assay with compound **9a** and confirm the mechanism. Moreover the overall study teaches us something more about the general picture of activity in this compound series:

Antitetrabenazine structure-activity relationships for piperidines **7-9** and **11** (Table I) are generally similar to relationships observed with the 3-arylspiro[isobenzofuran-1(3H),4'-piperidine-5']<sup>4</sup>. Thus, optimal activity appears to be associated with analogues where the nitrogen substituent is a hydrogen (**9a**) or a small alkyl group (**7a**). A larger nitrogen substituent (**7g** vs. **7a**) and N-hydroxylation (**11** vs. **9a**) lead to reduced activity. A basic nitrogen appears to be required for activity, as carbamate **8a** is essentially inactive. Significant antitetrabenazine activity is associated only with derivatives in which the phenylmethyl moiety is *ortho* rather than meta or para with respect to the piperidine ring (**7a** vs. **7b,c**; **9a** vs. **9b,c**). Selection of aromatic substituents (F, OCH<sub>3</sub>, and OH) was based on the observed activity of the corresponding 3-arylspiro[isobenzofuran-1(3H),4'-piperidines]. Tertiary amine derivatives with these substituents (**7d-f**) display reduced antitetrabenazine activity in comparison with **7a**, whereas the activity of secondary amine analogues is equipotent (**9d**), decreased (**9e**), and slightly enhanced (**9f**) in comparison with **9a**. The fact that an aromatic substituent frequently does not influence antitetrabenazine activity of tertiary and secondary amines in a similar manner was also reported for 3-arylspiro[isobenzofuran-1(3H),4'-piperidines]. Piperidines **7a** and **9a,d,f** display antitetrabenazine activity

Art Unit: 1625

comparable to imipramine or amitriptyline but are two to fourfold less potent than the analogous 3-arylspiro-[isobenzofuran-1(3H),4'-piperidines].

Piperidinols 3, esters 4, and ethers 5 (Table II) generally display weak antitetrabenazine activity, with the exception of 3d,h and 5c which exhibit modest activity. Benzyl ethers 13 (Table IV), at best, display modest activity, with tertiary amine 13d being approximately twice as potent as secondary amine 13a. Tetrahydropyridines 6 (Table III) also, at best, exhibit modest activity, with the exception of secondary amine 6h which is comparable to amitriptyline.

They teach that *ortho* substitution of the benzyl moiety is preferred, and that compounds 6h, 9a, 9d-9f are preferred compounds. In addition the authors state that “the fact that an aromatic substituent frequently does not influence antitetrabenazine activity of tertiary and secondary amines” which leads us to believe that the substituents on the aromatic ring are not important for activity.

Silverman, R.B. *The Organic Chemistry of Drug Design and Drug Action* 1992, Academic: New York, pg 19, teaches that “*Bioisosteres* are substituents or groups that have chemical or physical similarities, and which produce broadly similar biological properties.” He goes on to state Erlenmeyer’s 1948 definition of “classical isosteres” as “atoms, ions, or molecules in which the peripheral layers of electrons can be considered to be identical”. Table 2.2 lists several of these classical isosteres under heading 2, it is clear that the ether linkage (-O-) is a classical bioisostere of methylene (-CH<sub>2</sub>-).

B) The only difference between the compounds of the instant case and those of Martin et. al is the bioisosteric replacement of methylene -CH<sub>2</sub>. with an ether linkage (-O-). These compounds are shown side-by-side in Figure 3, for clarity.

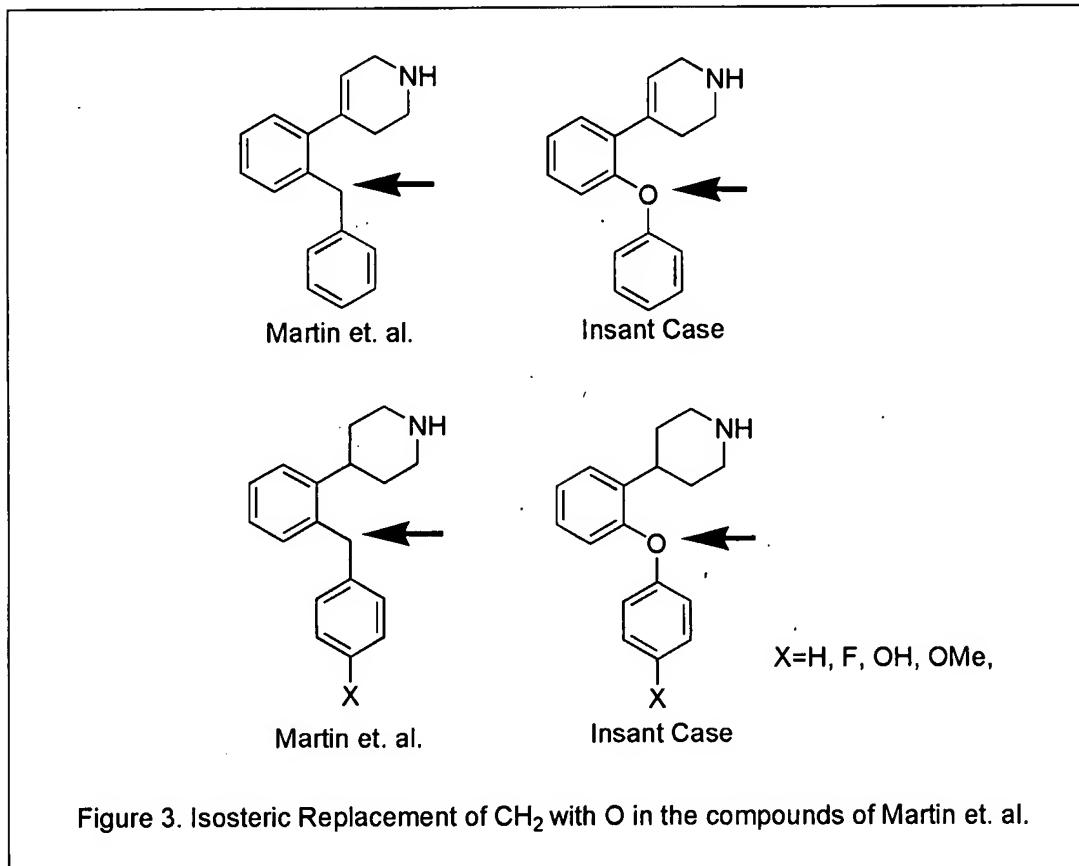


Figure 3. Isosteric Replacement of  $\text{CH}_2$  with O in the compounds of Martin et. al.

The other species claimed, differ only in the substituents in the aryl ring.

C) The level of ordinary skill in the art is high, and would be someone with synthetic chemistry experience and biochemistry. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these bioisosteres based on the expectation that such bioisosteres would have similar properties and upon the routine nature of such experimentation in the art of medicinal chemistry. Moreover Elliot et. al. PCT/IB00/00108 teaches that biaryloxyethers with a 2-piperidinyl moiety (Figure 2, structure I) are effective monoamine reuptake inhibitors. Thus this piece of information provides a strong motivation to make the change and one skilled in the art could expect an increase in potency in going from the methylene to O linkage. The courts have examined obviousness in a very similar situation *Mead*

*Johnson & Co. v. Premo Pharmaceutical Labs* 207 USPQ 820-852, where a bioisosteric replacement of methylene ( $\text{CH}_2$ ) with oxygen (O) was the issue and held that oxygen substituted compound Isoxsuprine was obvious over Nylidrin the methylene prior art compound, (Figure 4).

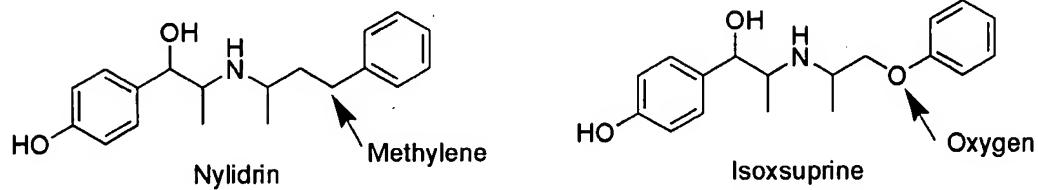


Figure 4. Compounds of *Mead Johnson & Co. vs. Premo Pharmaceuticals* 207 USPQ 820 (pg.825).

Here we have the prior art which teaches a very narrow set of compounds with the same utility. The modification [ $(\text{CH}_2)$  to (O)] was well known in the same very specific art (Elliot et. al. *vide supra*) and was the preferred or at the very least an alternative substituent. Thus a finding of obviousness is appropriate in this case.

#### *Conclusion*

10. No claims are allowed. This action is FINAL. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

DKO

  
Rita Desai

RITA DESAI  
PRIMARY EXAMINER

10/31/07

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D.K.O.